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(54) Stable polymorphic form of (E)-N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl) acrylamide and the process for its preparation.

(57) Stable and crystallographically essentially pure polymorphic form A of (E)-N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitro-phenyl)acrylamide may be prepared by crystallizing crude synthesis product from lower aliphatic carboxylic acid such as formic or acetic acid with a catalytic amount of hydrochloric or hydrobromic acid added. The product is a potent inhibitor of catechol-O-methyl-transferase enzyme (COMT).

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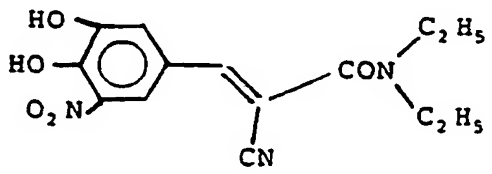
STABILE POLYMORPHIC FORM OF (E)-N,N-DIETHYL-2-CYANO-3-(3,4-DIHYDROXY-5-NITROPHENYL)ACRYLAMIDE AND THE PROCESS FOR ITS PREPARATION

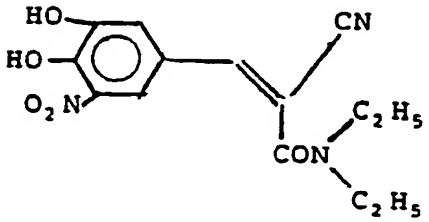
The present invention relates to the stabile and crystallografically essentially pure polymorphic form of N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide E-isomer, denoted (E)-N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide A, and to a process for the preparation thereof.

N,N-Diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide described in British Patent Application No. 8727854 by the applicant is a potent inhibitor of catechol-O-methyl-transferase enzyme (COMT) and may be used pharmaceutically in the treatment of e.g. Parkinson disease. This compound with melting point 153-156 °C has proved to be a mixture of two geometric isomers, E- and Z-isomers (70-80% E-isomer and 30-20% Z-isomer) having formulae:



I

E-isomer, m.p. 162 - 163°C



II

Z-isomer, m.p. 148 - 151°C

(E)-N,N-Diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide (I) may exist at least in two polymorphic forms A and B as shown by X-ray crystallography. The Z-isomer as well as the polymorphic form B of the E-isomer have been shown to be unstabile. The Z-isomer is transformed readily into the E-isomer on the influence of heat or acids. Similarily the polymorphic form B of the E-isomer isomerises slowly to the polymorphic form A on standing at room temperature. On recrystallization of the crude synthesis product from conventional solvents such as lower aliphatic alcohols, esters or hydrocarbons, e.g. ethanol, 2-propanol, ethyl acetate or toluene, a very complicated mixture of different geometric isomers and/or polymorphic forms are generally obtained which interfere with the characterization and standardization of the drug substance. The polymorphism and geometrical isomerism may also influence on the bioavailability of the drug.

Surprisingly it has now been observed that crystallographically essentially pure and stabile polymorphic form A of (E)-N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide is obtained in good yield, when the crude product of synthesis is recrystallized from a lower aliphatic carboxylic acid such as formic or acetic acid with a catalytic amount of hydrochloric or hydrobromic acid added. This method allows large scale production of homogenous and crystallographically essentially pure polymorphic form A of (E)-N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide independent of batch size or cooling rate.

"Crystallographically essentially pure" means here the polymorphic form A of (E)-N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide containing a maximum of 3% and preferably a maximum of 2%

of other polymorphic forms or Z-isomer.

"Lower aliphatic carboxylic acid" means here aliphatic carboxylic acid having 1-2 carbon atoms. Examples are formic and acetic acid.

The amount of hydrochloric or hydrobromic acid appropriate for use in crystallising the crude form of the product will vary depending on the exact proportion of isomers in the crude form. Typically hydrobromic acid will be used in a weight ratio of hydrobromic acid: carboxylic acid of 1:80 to 1:120, preferably about 1:100. Typically hydrochloric acid will be used in a weight ratio of hydrochloric acid: carboxylic acid of 1:180 to 1:220, preferably about 1:200.

The crystallization from the crude product takes place preferably by first admixing the crude product and the carboxylic acid and the hydrohalic acid in any order. Most conveniently the hydrohalic acid is first admixed with the carboxylic acid and the crude product then added, although other processes, e.g. the simultaneous admixing of the three components, is also envisaged.

The crude product is preferably used in a weight ratio of crude product to carboxylic acid of 1:1.5 to 1:4 more preferably 1:2 to 1:3.

The mixture is generally heated, preferably with stirring, to a temperature at which the crude product dissolves but below the boiling point of the mixture. Typically this is 80 to 98°C e.g. about 90°C. The solution is then slowly cooled to about 15-20°C and the crystalline product, essentially pure polymorphic form A, may be filtered and washed.

Table 1.

Typical IR-absorption bands of the polymorphic form A of (E)-N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide	
Wavenumbers (cm^{-1}) and the relative intensities of absorption bands	Assignment of the vibrational modes
3339 s	O-H stretching
3092 w 3066 w 3039 w	C-H stretching, aromatic and unsaturated
2981 w 2938 w	C-H stretching, saturated
2217 m 1628 s	CN stretching tertiary amide C=O stretching
1607 s 1580 sh	C=C stretching, conjugated with C=O and aromatic ring; and C=C stretching, aromatic
1544 s 1512 m 1441 s 1377 s	NO_2 assymetric stretching C=C stretching, aromatic CH_2 bending; assymetric CH_3 bending; C=C stretching, aromatic NO_2 symmetric stretching; OH bending
1298 s 1281 sh	C-O stretching
1210 m 1165 m 1150 m	C-H bending, aromatic
800 sh 779 m 740 m	C-H out of plane bending, aromatic
s = strong; m = medium; w = weak; sh = shoulder	

Experimental

Instrument: Perkin-Elmer FTIR 1725X
Detector: TGS
Ordinate mode: %T
Abscissa mode: Wavenumbers (cm^{-1})
Resolution: 4 cm^{-1}
Number of scans: 20
Phase KBr

The X-ray powder diffraction patterns of the polymorphic form A of (E)-N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide are seen in Figure 2 and the crystallographic data in Table 2.

Table 2.

Crystallographic data of polymorphic form A of (E)-N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide			
Peak positions (2θ), interplanar spacings (d) and relative peak intensities of the first 20 reflections.			
No	2θ	d	Rel I (%)
1	3.680	23.9905	0.8
2	9.040	9.7745	49.7
3	11.840	7.4685	9.9
4	13.541	6.5339	11.1
5	14.060	6.2939	11.6
6	15.820	5.5974	7.6
7	16.320	5.4270	3.9
8	18.220	4.8651	4.6
9	18.459	4.8027	8.7
10	18.720	4.7363	13.6
11	18.940	4.6818	5.5
12	20.041	4.4270	5.0
13	20.380	4.3541	11.1
14	21.140	4.1993	3.5
15	21.939	4.0481	58.3
16	22.901	3.8802	13.8
17	23.340	3.8082	100.0
18	23.960	3.7110	3.3
19	24.480	3.6334	2.9
20	26.343	3.3805	3.6

Experimental

Instrument: Siemens D500
Wavelength: 0.1541 nm (Cukα_1)
Range: 3° - 33° (2θ)
Power: 40 mA/40 kV
Time: 1°/min (0.02°/step)

The following example illustrates the invention.

Example 1;

The crude synthesis product (3.0 kg) prepared according to the method described in British Patent Application 8727854 was dissolved in 8.0 kg of acetic acid (98-100%) (or formic acid) containing 80 g of hydrogen bromide (or 40 g of hydrogen chloride) by heating to 90 °C). The solution was slowly cooled to 20 °C and stirred for 20 h at 20 °C and finally for 6 h at 15 °C. The crystalline product was filtered and washed carefully first with a cold (4 °C) mixture (1 l) of toluene-acetic acid (1:1 v/v) and then with cold toluene (1 l). The product was dried in vacuum at 45 °C. Yield of crystallografically pure A form of (E)-N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide was 2.4 kg (80%), m.p. 162-163 °C.

Claims

1. The crystallographically essentially pure polymorphic form A of (E)-N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide characterized by the infrared spectrum in potassium bromide having the following absorption bands:

Wavenumbers (cm^{-1})	Wavenumbers (cm^{-1})
3339	1512
3092	1441
3066	1377
3039	1298
2981	1281
2938	1210
2217	1165
1628	1150
1607	800
1580	779
1544	740

2. A process for preparing the crystallographically essentially pure polymorphic form A of (E)-N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide of claim 1 which comprises crystallization of crude N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide from a lower aliphatic carboxylic acid containing a catalytic amount of hydrochloric or hydrobromic acid.

3. The process as claimed in claim 2, wherein said lower aliphatic carboxylic acid is acetic acid.

4. The process as claimed in claim 2, wherein said lower aliphatic carboxylic acid is formic acid.

Claims for the following Contracting States: ES,GR

1. A process for preparing the crystallographically essentially pure polymorphic form A of (E)-N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-acrylamide characterized by the infrared spectrum in potassium bromide having the following absorption bands:

WAVENUMBERS (cm^{-1})	WAVENUMBERS (cm^{-1})
3339	1512
3092	1441
3066	1377
3039	1298
2981	1281
2938	1210
2217	1165
1628	1150
1607	800
1580	779
1544	740

which comprises crystallization of crude N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide from a lower aliphatic carboxylic acid containing a catalytic amount of hydrochloric or hydrobromic acid.

2. The process as claimed in claim 1, wherein said lower aliphatic carboxylic acid is acetic acid.

3. The process as claimed in claim 1, wherein said lower aliphatic carboxylic acid is formic acid.

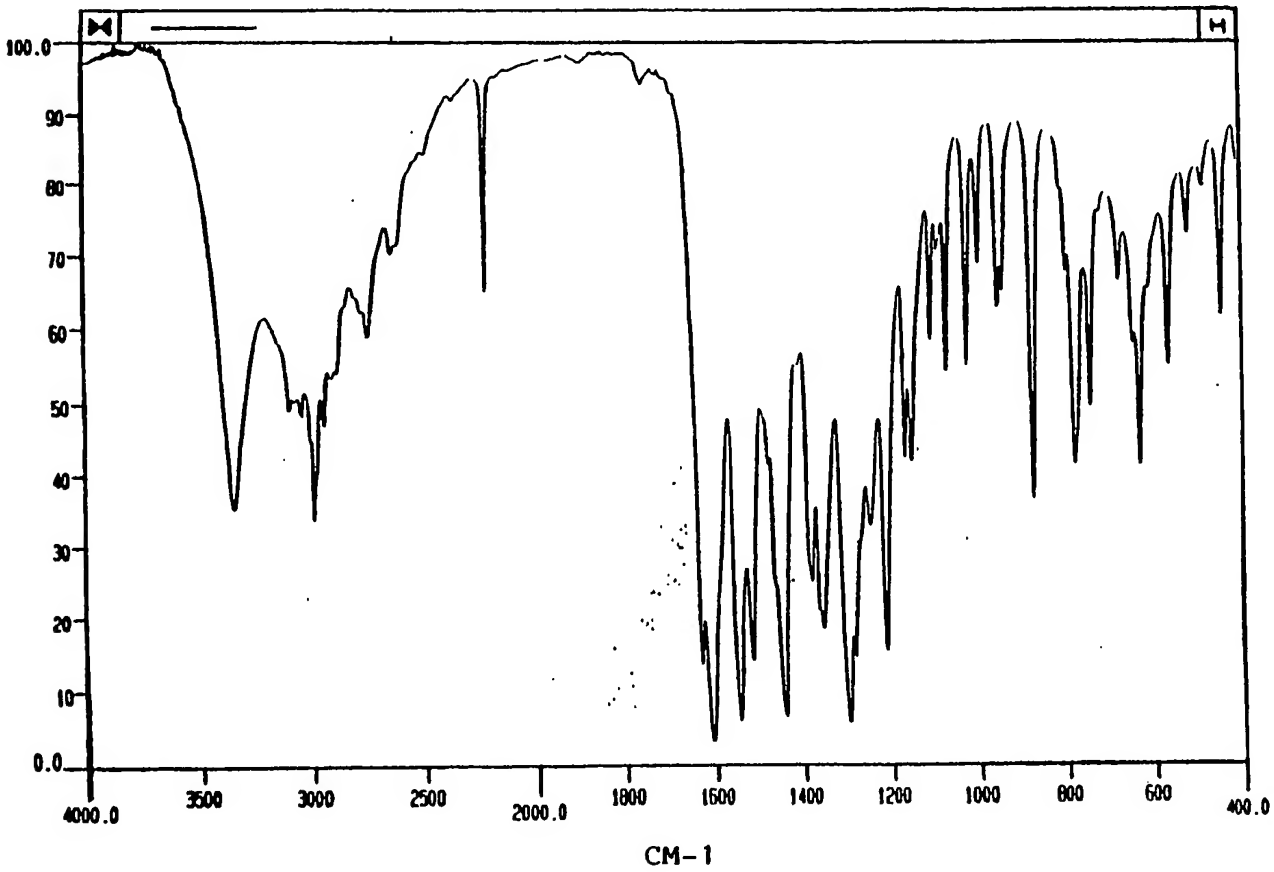


FIGURE 1. IR-spectrum of the polymorphic form A of (E)-N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide.

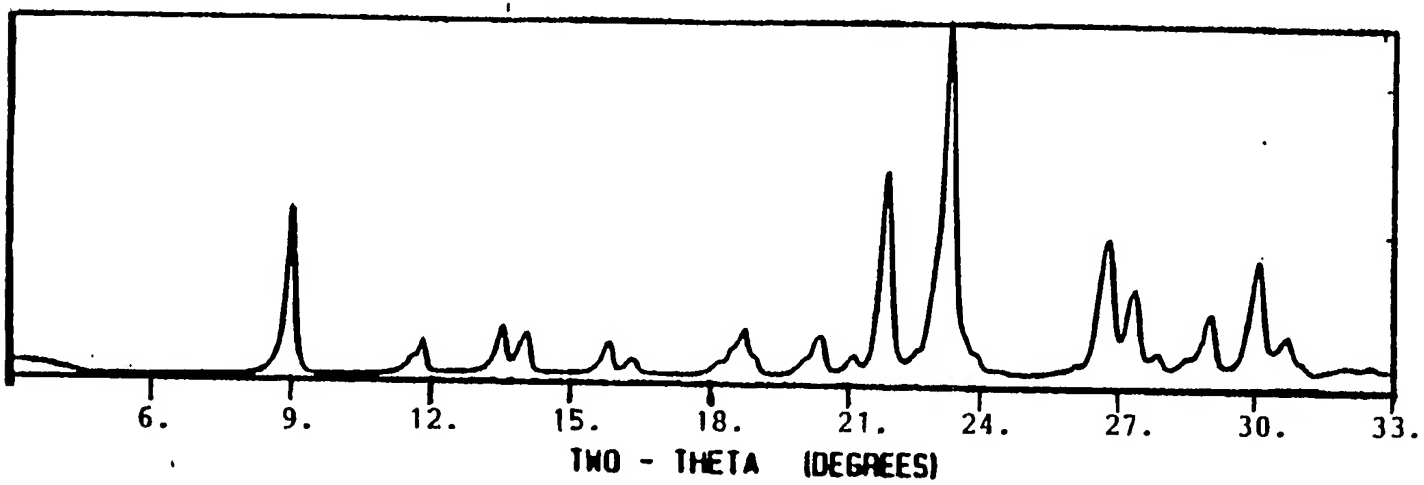


FIGURE 2. Standard X-ray powder diffraction pattern of the polymorphic form A of (E)-N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide.

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EUROPEAN SEARCH REPORT

Application Number

EP 90 31 1963

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	FR-A-2 607 493 (ORION-YHTYMA OY.) * page 57, example 100; claims 21-23 *	1-4	C07C255/41

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

C07C

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	06 MARCH 1992	ZERVAS B.

CATEGORY OF CITED DOCUMENTS

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